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PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

COLB, Sanford T.
SANFORD T. COLB & CO.
P.O. Box 2273
Rehovot 76122
ISRAEL

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT
(PCT Rule 71.1)

	Date of mailing *(day/month/year)* 18.01.2001	
Applicant's or agent's file reference 36220	**IMPORTANT NOTIFICATION**	
International application No. PCT/IL99/00645	International filing date *(day/month/year)* 30/11/1999	Priority date *(day/month/year)* 01/12/1998
Applicant YEDA RESEARCH AND DEVELOPMENT CO. LTD. et al.		

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/ European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Benigar, M Tel.+49 89 2399-2996

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 18 July 2000 (18.07.00)	
International application No. PCT/IL99/00645	**Applicant's or agent's file reference** 36220
International filing date (day/month/year) 30 November 1999 (30.11.99)	**Priority date** (day/month/year) 01 December 1998 (01.12.98)
Applicant KAM, Zvi et al	

1. The designated Office is hereby notified of its election made:

   [X] in the demand filed with the International Preliminary Examining Authority on:

   05 June 2000 (05.06.00)

   [ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was [ ] was not

   made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland** Facsimile No.: (41-22) 740.14.35	Authorized officer Nestor Santesso Telephone No.: (41-22) 338.83.38

new

TENT COOPERATION TR Y

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WIPO PCT

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 36220	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/IL99/00645	International filing date *(day/month/year)* 30/11/1999	Priority date *(day/month/year)* 01/12/1998
International Patent Classification (IPC) or national classification and IPC G06T1/00		
Applicant YEDA RESEARCH AND DEVELOPMENT CO. LTD. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 10 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   I ☒ Basis of the report
   II ☐ Priority
   III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   IV ☒ Lack of unity of invention
   V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   VI ☐ Certain documents cited
   VII ☐ Certain defects in the international application
   VIII ☒ Certain observations on the international application

Date of submission of the demand 05/06/2000	Date of completion of this report 18.01.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Casteller, M Telephone No. +49 89 2399 2666

Form PCT/IPEA/409 (cover sheet) (January 1994)

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:

Description, pages:

1-15 as originally filed

Claims, No.:

1-37 as originally filed

Drawings, sheets:

1/8-8/8 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☒ complied with.

   ☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☒ all parts.

   ☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-37
	No:	Claims	
Inventive step (IS)	Yes:	Claims	30, 32
	No:	Claims	1-29, 31, 33-37

Industrial applicability (IA)	Yes:	Claims	1-37
	No:	Claims	

2. Citations and explanations
   see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item IV
Lack of unity of invention

1. The International Preliminary Examining Authority does not agree with the objection put forward by the International Search Authority as to lack of unity of invention (Rule 13.1 PCT) for the following reasons.
   In the International Search Report (transmitted on 22.06.2000), the following four inventions groups were identified:

   first invention (claims 1-29): an apparatus (claims 1-17) and a method (claims 18-29) for computational adaptive imaging including:
   an image information acquirer providing refractive characteristics of an imaged volume,
   a ray tracer providing a location-dependent PSF (Point Spread Function) from said provided refractive characteristics, and
   a deconvolver utilising said location-dependent PSF to provide an output image corrected for distortions;

   second invention (claims 30-33): an apparatus (claims 30, 31) and a method (claims 32, 33) for providing 3D refractive index information of an imaged object from DIC (Differential Interference Contrast) images thereof by means of a line integrator and then providing a plurality of 2D representations of the refractive index of the object;

   third invention (claims 34, 35): apparatus and method for ray tracing through a medium having known (claim 34) or determined (claim 35) point-to-point variations in refractive index;

   fourth invention (claims 36, 37): apparatus and method for confocal microscopy including a ray tracer determining an aberrated wavefront from known (claim 36) or determined (claim 37) point-to-point variations in refractive index, said aberrated wavefront being used in an adaptive optical element to correct aberrations.

2. The problem common to all four claimed inventions is considered to be the **determination of 3D refractive index information of an imaged biological**

sample, which is then used to adaptively correct aberrations. Despite of the unclear and confusing wording of the claims (see Section VIII below), all independent claims contain in various forms a reference to this feature which is considered to be a "special technical features" (STF) as defined in Rule 13.2 PCT, that is, a feature that defines a contribution which each of the claimed inventions, considered as a whole, makes over the prior art.

Re Item V
Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

3. Reference is made to the following documents:

D1: GB-A-2 321 968 (INSTUT FRANCAIS DU PETROL)
D2: B.A. SCALETTAR et al.: "Dispersion, aberration and deconvolution in multi-wavelength fluorescence images", JOURNAL OF MICROSCOPY, vol. 182, no. 1, April 1996 (1996-04), pages 50-60, XP000879385

4. In the International Search Report, document D1 was (apparently) considered to be the closest prior art. However, this document belongs to a technical field (geological prospection by seismic data processing) so far away from the filed of the invention (microscopical imaging) that the skilled person would unlikely turn to it when looking for a solution to the above mentioned problem, and, even if he or she would, it would be evident that the data which are processed (being collected by a limited number of sensor and in which the time factor is essential) are so different from the images collected by the CCD camera of the invention that there is in fact no mention in D1 of the PSF.
The closest prior art is instead considered to be represented by document D2.
D2 shows that there was awareness in the field of optical microscopy of the necessity of determining an appropriate PSF (cf. D2, page 51, right column, lines 29-32) for the overall imaging system, in order to be able to deblur the images by deconvolution (cf. D2, page 52, right column, lines 1-12). To this end, various techniques were known for determining the PSF of the imaging system itself (i.e. lenses, immersion oils, etc. cf. D2, page 51, last paragraph of the left column and first paragraph of the right

column, page 53, last full paragraph).
It was of course known that the sample itself, that is, its 3D refractive index, also determines the PSF of the imaging system (cf. D2, "the characteristics of the PSF are essentially determined by the optical properties of the sample and the objective lens", page 53, last full paragraph), **but D2 declaredly fails to indicate adequate solutions to this problem**: cf. D2, page 56, left column, second last paragraph ("for PSF images [...] for a typical biological image an appropriate OTF is not so easily identified").

5. It is noted that the following elements of the invention are, at least when considered in isolation, known from the prior art.
As acknowledged in the application itself (cf. paragraph bridging pages 10 and 11), once an adequate PSF of the imaging system including the effects caused by the varying refractive index of the sample itself is provided, it is known (e.g. from D2, page 52, right column, lines 1-12) to provide an output image corrected for distortions by deconvolution. The subject-matter of the last three lines of e.g. claims 1 and 18 is thus, in itself, known.
Furthermore, once the point-to-point variations in refractive index of a sample are provided, ray tracing techniques for determining an aberrated wavefront in the sample are known, as acknowledged in the application itself (cf. page 14, lines 8-9), as well as further methods for determining the 3D PSF of the sample from this aberrated wavefront (cf. page 14, lines 12-13). Hence the subject-matter of e.g. lines 4-7 of claims 1 and 18, claim 34, lines 3-5, claim 35, lines 5-6, claim 36, lines 2-5, claim 37, lines 4-6, is, in itself, known.

6. The invention combines these known techniques with novel means and steps for determining said point-to-point variations in refractive index of a sample.

6.1 According to the invention, an image information acquirer (10, 32) provides a plurality of 3D differential interference contrast (DIC) images (40, 42) of the sample, in which images a directional derivative of the refractive index in the sample is displayed (cf. e.g. the paragraph bridging pages 12 and 13 and claims 30 and 32), and a line integrator (34) provides (44) a plurality of 3D representations (46) of the refractive index of the sample from said DIC images by inverting the directional derivative of refractive index in said DIC images (cf. e.g. claims 30 and 32).

6.2 The invention then **inventively** exploits a combination of techniques, each being, in itself, **conventional** (cf. paragraph 5 above) for
utilizing the provided 3D representations of the refractive index to trace (48) a multiplicity of rays from a multiplicity of locations in the sample by means of a ray tracer (34) (cf. e.g. lines 4-6 of claims 1 and 18), thereby providing an aberrated wavefront (fig. 5) (cf. e.g. lines 6-7 of page 14),
the aberrated wavefront is integrated (50) to provide a location dependent point spread function (52, 84), (cf. e.g. line 7 of claims 1 and 18, and lines 6-8 of page 13) and
said point spread function is utilized (54) by a deconvolver (34) to provide an output image (56) corrected for distortion (cf. e.g. lines 8-10 of claims 1 and 18).

7. However, none of present independent claims 1, 18, 30, 32, 34, 35, 36 and 37 recites each and every of the essential characterizing invention features mentioned in above paragraph 6. Some of said essential features are instead only mentioned in the description and some other are sparsely mentioned in some of said independent claims.
It consequently appears that the present international application, considered as a whole, does disclose novel and inventive materials.
However, the subject-matter of independent claims 1, 18 and 34 to 37 does not meet the requirements of Article 33(3) PCT because they only recite various combinations of conventional techniques (cf. paragraph 6.2 above), each being known when considered in isolation.
The features recited in independent claims 30 and 32 are not directly or indirectly derivable in any available prior art document. As independent claims 30 and 32 at least mention some of the novel and inventive features characterizing the invention (cf. paragraph 6.1 above), they meet the requirements of Article 33(3) PCT, at least formally.
It is however considered that the invention as a whole is constituted not only by the features of claims 30 and 32, but by the inventive combination of these latter features with those sparsely recited in said independent claims 1, 18 and 34 to 37.
Dependent claims 2-17, 19-29, 31 and 33 apparently refer to implementation details and additional features of the invention which add nothing inventive to the subject-matter of the claims from which they depend. Whenever the parent independent claim does not meet the inventive step requirements of Article 33(3) PCT, these

requirements would also not be met by an independent claim amended so as to include the subject-matter of said dependent claims.

Re Item VIII
Certain observations on the international application

8. The application contains 8 independent claims having only partially overlapping scope. It does not seem that such a multiplicity of independent claims is necessary and hence the number of independent claims would not appear to be reasonable (Rule 6.1 (a) PCT); furthermore the claims themselves are not clear and concise, so that the requirements of Article 6 PCT are not met.
The claim set should have only included the minimum number of independent claims necessary to clearly and sufficiently define the invention, with dependent claims as appropriate, Article 6 and Rule 6.4 PCT.
The particular combination of features making up the invention as outlined in paragraph 6 above should have been included into one only independent claim per category.
The claims should have been provided with reference signs placed in parentheses (Rule 6.2(b) PCT).
To meet the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in document D2 and the improvements provided by the invention should have been discussed in the description.

9. According to dependent claims 13, 16 and 26, the principles of the invention could be applied to non-electromagnetic images, i.e. acoustic (seismic) images.
This can not be believed because the law of physics governing the transmission of sound through solid materials are different from those of light transmission.
In the introductory portion of the description (pages 5 and 7) the wording of these claims is merely repeated, but the detailed description does not support the claimed applicability of the invention to the processing of acoustic images.
It is therefore objected that the scope of dependent claims 13, 16 and 26 is unclear (Article 6 PCT) because they are not fully supported by the description, and that since the description does not even mention how to apply the invention to acoustic images, the application does not disclose the invention claimed in said claims in a

manner sufficiently clear and complete it to be carried out by a person skilled in the art (Article 5 PCT).

PATENT COOPERATION TREATY

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INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
36220		
International application No.	International filing date (*day/month/year*)	(Earliest) Priority Date (*day/month/year*)
PCT/IL 99/00645	30/11/1999	01/12/1998
Applicant		
YEDA RESEARCH AND DEVELOPMENT CO. LTD. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

      ☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

      ☐ contained in the international application in written form.
      ☐ filed together with the international application in computer readable form.
      ☐ furnished subsequently to this Authority in written form.
      ☐ furnished subsequently to this Authority in computer readble form.
      ☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
      ☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☐ **Certain claims were found unsearchable** (See Box I).

3. ☒ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 1b

   ☐ as suggested by the applicant.
   ☒ because the applicant failed to suggest a figure.
   ☐ because this figure better characterizes the invention.

   ☐ None of the figures.

Form PCT/ISA/210 (first sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IL 99/00645

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G06T1/00 G02B21/14 G02B21/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 G06T G02B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GB 2 321 968 A (INST FRANCAIS DU PETROL) 12 August 1998 (1998-08-12) page 4, line 11 -page 5, line 1 page 9, line 9 -page 18, line 16 ---	1,13,16, 18,26
A	US 5 671 136 A (WILLHOIT JR LOUIS E) 23 September 1997 (1997-09-23) abstract; figures 3,4 column 14, line 66 -column 15, line 7 --- -/--	1,13,16, 18,26

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 March 2000	22.06.00

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	SCHEU, M

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	B.A. SCALETTAR ET AL: "Dispersion,abberation and deconvolution in multi-wavelength fluorescence images" JOURNAL OF MICROSCOPY, vol. 182, no. 1, April 1996 (1996-04), pages 50-60, XP000879385 cited in the application page 50, left-hand column page 57, left-hand column, last paragraph -page 59 ---	1,2,10, 14, 17-19,24
A	US 5 787 146 A (GIEBELER ROBERT H) 28 July 1998 (1998-07-28) column 10, line 38 -column 12, line 5 ---	1,11,17, 18,24
A	PATENT ABSTRACTS OF JAPAN vol. 1997, no. 08, 29 August 1997 (1997-08-29) & JP 09 105864 A (OLYMPUS OPTICAL CO LTD), 22 April 1997 (1997-04-22) abstract & US 5 969 855 A (ITOH MASAHIDE ET AL.) 19 October 1999 (1999-10-19) column 2, line 65 -column 3, line 3 column 4, line 1 - line 26 ---	1,2,11, 17,18,24
A	AGARD D A ET AL: "Three-dimensional microscopy: image processing for high resolution subcellular imaging" NEW METHODS IN MICROSCOPY AND LOW LIGHT IMAGING, SAN DIEGO, CA, USA, 8-11 AUG. 1989, vol. 1161, pages 24-30, XP000879382 Proceedings of the SPIE - The International Society for Optical Engineering, 1989, USA ISSN: 0277-786X cited in the application page 24 -page 25, paragraph 2 page 27, paragraph 2 ---	1,11,18, 24
P,A	KAM Z: "MICROSCOPIC DIFFERENTAIL INTERFERENCE CONTRAST IMAGE PROCESSING BY LINE INTEGRATION (LID) AND DECONVOLUTION" BIOIMAGING,GB,IOP PUBLISHING, vol. 6, no. 4, December 1998 (1998-12), pages 166-176, XP000879404 ISSN: 0964-1726 cited in the application the whole document -----	1-37

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International application No.
PCT/IL 99/00645

INTERNATIONAL SEARCH REPORT

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [ ] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet(s)

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-29

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 1-29

Apparatus for computational adaptive imaging including an image information acquirer, a ray tracer providing a location dependent point spread function and a deconvolver utilizing the location dependent point spread function to provide a corrected output image.

2. Claims: 30-33

Apparatus and method for utilizing differential interference contrast images to provide three-dimensional refractive index information including a line integrator and a directional derivative

3. Claims: 34-35

Apparatus and method for ray tracing through a medium having multiple variations in refractive index including the determination of the refractive index at a multiplicity of locations in the medium

4. Claims: 36-37

Apparatus for confocal microscopy including a ray tracer and adaptive optics

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB 2321968 A	12-08-1998	FR 2759172 A	07-08-1998
		CA 2226389 A	05-08-1998
		NL 1008193 C	07-08-1998
		NO 980493 A	06-08-1998
US 5671136 A	23-09-1997	AU 1022597 A	03-07-1997
		WO 9722077 A	19-06-1997
US 5787146 A	28-07-1998	NONE	
JP 09105864 A	22-04-1997	US 5969855 A	19-10-1999

U 013475-2

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : G06T 1/00, G02B 21/14, 21/00 — A2

(11) International Publication Number: WO 00/33250

(43) International Publication Date: 8 June 2000 (08.06.00)

(21) International Application Number: PCT/IL99/00645

(22) International Filing Date: 30 November 1999 (30.11.99)

(30) Priority Data:
127359 — 1 December 1998 (01.12.98) — IL
09/238,225 — 27 January 1999 (27.01.99) — US

(81) Designated States: CA, IL, JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
Without international search report and to be republished upon receipt of that report.

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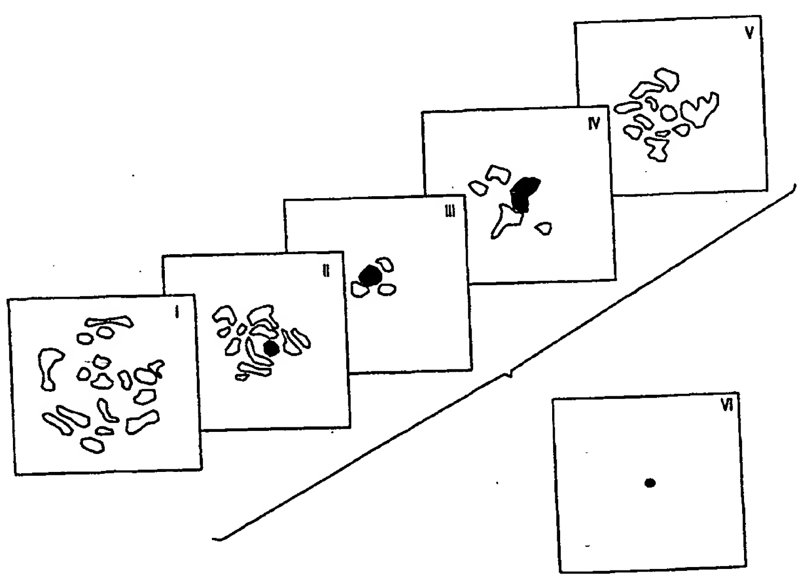
(54) Title: COMPUTERIZED ADAPTIVE IMAGING



(57) Abstract

Apparatus for computational adaptive imaging comprises the following: an image information acquirer, which provides information relating to the refractive characteristics in a three–dimensional imaged volume; a ray tracer, which uses the information relating to the refractive characteristics to trace a multiplicity of rays from a multiplicity of locations in the three–dimensional imaged volume through the three–dimensional imaged volume, thereby providing a location dependent point spread function, and a deconvolver, which uses the location dependent point spread function, to provide an output image corrected for distortions due to variations in the refractive characteristics in the three–dimensional imaged volume.

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COMPUTERIZED ADAPTIVE IMAGING

FIELD OF THE INVENTION

The present invention relates to imaging generally and more particularly to post acquisition image processing generally.

BACKGROUND OF THE INVENTION

Post acquisition image processing is well known in the literature. Publications which describe the general state of the art in post acquisition image processing are : Lim, J.S. "Two dimensional signal and image processing". Englewood Cliffs, NJ. Prentice Hall. (1990); Russ, J.C. "Image processing handbook". CRC Press. (1992); Pratt, W.K. "Digital image processing". NY John Wiley & Sons, Inc. (1991); Rosenfeld, A. and Kak, A.C. "Digital picture processing". Academic Press. (1976); Castleman, K.R. "Digital Image Processing". Prentice-Hall Inc. Englewood Cliffs, New Jersey. (1979).

Imaging which provides information relating to refractive characteristics in a imaged volume is known for extremely limited applications. In microscopy, Smith, Nomarski and Differential Interference Contrast (DIC) imaging is known and is described in the following publications: Nomarski, G. "Microinterferometre differential a ondes polarisees". J. Phys. Radium 16:9S-11S (1955); Lang, W. "Differential-Interferenz-Miikroskopie". Carl-Zeiss, Oberkochen (1975); Inoui, S. and Spring, K.S. "Video Microscopy: the fundamentals". 2nd edition. Plenum Press, NY. (1997). Tanford, C. "Physical chemistry of macromolecules". John Wiley NY. (1961). Appendix C describes classical Rayleigh interference methods, Philpot and Svenson methods based on schlieren image, Lamm method of line displacement, and Gouy interference method all developed for determination of one dimensional refractive index variations.

Computer analysis of DIC imaging is not readily achieved. Known instances are described in the following publications: Allen, R.D., Allen, N.S. and Travis,

J.L. "Video-enhanced contrast, differential interference contrast (AVEC-DIC) microscopy: a new method capable of analyzing microtubule related motility in the reticulopodial network of Allogromia laticollaria." Cell Motility 1: 291-302 (1981); Cogswell, C.J. and Sheppard, C.J.R. "Confocal differential interference contrast (DIC) microscopy: including a theoretical analysis of conventional and confocal DIC imaging". J. Microsc. 165:81-101 (1992); Gelles, J., Schnapp, B.J. and Sheetz, M.P. "Tracking kinesin-driven movements with nanometre-scale precision", Nature 331:450-453 (1988); Hdusler, G. and Kvrner, E. "Imaging with expanded depth of focus". Zeiss Inform. 29: 9-13 (1987); Preza, C., Snyder, D.L. and Conchello, J-A. "Image reconstruction for three-dimensional transmitted light DIC microscopy". SPIE 2984:220-231 (1997);.Schormann, T. and Jovin, T.M. "Contrast enhancement and depth perception in three-dimensional representations of differential interference contrast and confocal scanning laser microscope images". J. Microsc. 166:155-168 (1992).

Computerized ray tracing between discrete refractive and reflective surfaces is extremely well developed, but is not well known in the environment of non-homogeneous indices of refraction. This area is described in the following publications: Hecht E. and Zajac A. "Optics" 2nd ed. Addison-Wesley Reading MA (1997); Jenkins, F.A, and White, H.E. "Fundamentals of optics". McGraw-Hill, NY (1950) ch.8: Ray Tracing.

Calculation of point spread functions (PSF) is extremely well known as described in the following publication: Born M. and Wolf E. "Principles of Optics" Pergamon London (1959);Goodman J.W. "Statistical Optics" John Wiley & Sons NY (1985);Hecht E. and Zajac A. "Optics" 2nd ed. Addison-Wesley Reading MA. (1997); Gibson S.F. and Lanni F. "Diffraction by circular aperture as a model for three-dimensional optical microscopy". Opt. Soc. Am. A 6:1357-1367 (1989); Gibson S.F. and Lanni F. "Modeling aberrations due to mismatched layers for 3-D microscopy" SPIE optics in complex systems 1319:470-471 (1990); Gibson S.F. and Lanni F. "Experimental test of an analytical model of aberration in an oil-immersion objective lens used in three-dimensional light microscopy". J. Opt. Soc. Am. A 8:1601-1613 (1991).

Deconvolution of three dimensional microscopic images having location

independent PSF is well known and is described in the following publications, some of them authored by some of the present inventors: Jansson, P.A. ed. "Deconvolution of images and spectra". Academic Press NY (1997); Agard, D.A. and Sedat, J.W.. "Three-dimensional architecture of a polytene nucleus". Nature 302:676-681 (1984); Agard, D.A., Hiraoka, Y., Shaw, P. and Sedat, J.W. "Fluorescence microscopy in three dimensions". Methods in Cell Biology 30: 353-377 (1989); Castleman, K.R. "Digital Image Processing". Prentice-Hall Inc. Englewood Cliffs, New Jersey (1979). Correction of telescopic images by the use of suitably distorted mirrors and deconvolution of two dimensional telescope images having location dependent PSF are described in the following publications: Boden, A.F., Reeding, D.C, Hanisch, R.J., Mo, J. and White, R. "Comparative results with massively parallel spatially-variant maximum likelihood image restoration". Bul Am Astr. Soc 27:924-929 (1995); Boden, A.F., Reeding, D.C, Hanisch, R.J. and Mo, J. "Massively parallel spatially-variant maximum likelihood restoration of Hubble space telescope imagery". J Opt Soc Am A 13: 1537-1545 (1996); Jansson, P.A. ed. "Deconvolution of images and spectra". Academic Press NY (1997); Tyson R.K. "Principles of Adaptive Optics" Academic Press NY (1991). Reconstruction of blurred images from point objects is described in the following publications: Carrington, W.A., Lynch, R.M., Moore, D.W., Isenberg, G., Fogarty, K.E. and Fay, F.S. "Superresolution three-dimensional images of fluorescence in cells with minimal light exposure". Science 268:1483-1487 (1995); Femino, A.M., Fay, F.S., Fogarty, K., and Singer, R.H. "Visualization of single RNA transcripts in situ". Science 280:585-590 (1998).

SUMMARY OF THE INVENTION

The present invention seeks to provide improved apparatus and techniques for post acquisition image processing.

There is thus provided in accordance with a preferred embodiment of the present invention apparatus for computational adaptive imaging including an image information acquirer providing information relating to the refractive characteristics in a three-dimensional imaged volume, a ray tracer, utilizing the information relating to the

refractive characteristics to trace a multiplicity of rays from a multiplicity of locations in the three-dimensional imaged volume through the three-dimensional imaged volume, thereby providing a location dependent point spread function and a deconvolver, utilizing the location dependent point spread function, to provide an output image corrected for distortions due to variations in the refractive characteristics in the three-dimensional imaged volume.

Preferably, the image information acquirer acquires at least two three-dimensional images of a three-dimensional imaged volume, at least one of the two three-dimensional images containing the information relating to the refractive characteristics in a three-dimensional imaged volume.

When the refractive characteristics are extractable from the image to be corrected for distortions, or are known independently, only one three-dimensional image need be acquired.

The acquirer may obtain refractive index information from DIC, for example from phase microscopy or from fluorescence -for example in DNA associated stains wherein the stain intensity is proportional to the refractive index increment.

Refractive index mapping may be applied to samples whose refractive index is known. For example this may apply to microchip wafer structures, whose geometry is known.

In accordance with a preferred embodiment of the present invention, the image acquirer acquires at least three three-dimensional images of the three-dimensional imaged volume.

Preferably, the image acquirer acquires a plurality of three-dimensional images of the three-dimensional imaged volume, each the image having a discrete wavelength band.

Alternatively, the image acquirer acquires a multiplicity of three-dimensional images of the three-dimensional imaged volume, each the image having a wavelength band which is part of a continuum represented by the wavelength bands of the multiplicity of three-dimensional images.

In accordance with a preferred embodiment of the present invention, the

ray tracer and the deconvolver utilize the information relating to the refractive characteristics in a three-dimensional imaged volume obtained from one of the three-dimensional images to correct at least another one of the three-dimensional image or itself.

The acquirer may obtain refractive index information from DIC, or from phase microscopy or from fluorescence -for example in DNA associated stains wherein the stain intensity is proportional to the refractive index increment.

Refractive index mapping may be applied to samples whose refractive index is known. For example this may apply to microchip wafer structures, whose geometry is known.

According to one embodiment of the present invention, the three-dimensional images are electromagnetic energy images. Preferably, the three-dimensional images are infrared images.

Alternatively, the three-dimensional images are non-electromagnetic images.

In accordance with a preferred embodiment of the present invention, the image acquirer receives digital image data from a digital image source and derives therefrom the information relating to the refractive characteristics in a three-dimensional imaged volume.

Preferably, the ray tracer and the deconvolver operate repeatedly over time to provide a multiplicity of output images, each corrected for distortions due to variations in the refractive characteristics in the three-dimensional imaged volume. Such a deconvolution process can be iteratively applied to the whole process to improve the estimation of the refractive index.

In accordance with one embodiment of the present invention, the output image is an acoustic image and the refractive characteristics are characteristics of a material which the passage of acoustic energy therethrough.

In accordance with an alternative embodiment of the present invention, the output image is an electromagnetic image and the refractive characteristics are characteristics of a material which the passage of electromagnetic energy therethrough.

There is also provided in accordance with a preferred embodiment of the present invention a method for computational adaptive imaging including the steps of:

providing information relating to the refractive characteristics in a three-dimensional imaged volume;

ray tracing, utilizing the information relating to the refractive characteristics, a multiplicity of rays from a multiplicity of locations in the three-dimensional imaged volume through the three-dimensional imaged volume, thereby providing a location dependent point spread function; and

deconvoluting, utilizing the location dependent point spread function, thereby providing an output image corrected for distortions due to variations in the refractive characteristics in the three-dimensional imaged volume. Such a deconvolution process can be iteratively applied to the whole process to improve the estimation of the refractive index.

Preferably, the step of providing information includes acquiring at least two three-dimensional images of a three-dimensional imaged volume, at least one of the two three-dimensional images containing the information relating to the refractive characteristics in a three-dimensional imaged volume.

When the refractive characteristics are extractable from the image to be corrected for distortions, or are known independently, only one three-dimensional image need be acquired.

In accordance with a preferred embodiment of the present invention, the step of providing information includes acquiring at least three three-dimensional images of a three-dimensional imaged volume.

Preferably, the step of providing information includes acquiring a plurality of three-dimensional images of the three-dimensional imaged volume, each image having a discrete wavelength band.

In accordance with a preferred embodiment of the present invention, the step of providing information includes acquiring a multiplicity of three-dimensional images of the three-dimensional imaged volume, each the image having a wavelength band which is part of a continuum represented by the wavelength bands of the

multiplicity of three-dimensional images.

In accordance with one embodiment of the present invention, the three-dimensional images are electromagnetic energy images. Preferably, the three-dimensional images are infrared images.

In accordance with an alternative embodiment of the present invention, the three-dimensional images are non-electromagnetic images.

The refractive index may be in any medium and the imaging method may be for a generalised method for inhomogeneous media that may distort the image.

Preferably, the step of providing includes receiving digital image data from a digital image source and deriving therefrom the information relating to the refractive characteristics along a multiplicity of light paths in a three-dimensional imaged volume.

In accordance with a preferred embodiment of the present invention, the steps of providing information, ray tracing and deconvoluting operate repeatedly over time to provide a multiplicity of output images, each corrected for distortions due to variations in the refractive characteristics in the three-dimensional imaged volume. Such a deconvolution process may be iteratively applied to the whole process to improve the estimation for the refractive index map.

There is also provided in accordance with a preferred embodiment of the present invention apparatus for utilizing differential interference contrast images to provide three-dimensional refractive index information including a line integrator operating on differential interference contrast images displaying a directional derivative of refractive index of an object to invert the directional derivative thereof, thereby providing a plurality of two-dimensional representations of the refractive index of the object. Alternatively the three-dimensional refractive index map can be obtained from phase microscopy, or from fluorescence where the staining is proportional to the refractive index increment.

There is additionally provided in accordance with a preferred embodiment of the present invention apparatus for utilizing differential interference contrast images to provide three-dimensional refractive index information and also including a deconvolver

performing deconvolution of the plurality of two-dimensional representations of the refractive index of the object, thereby reducing out-of-focus contributions to the two-dimensional representations of the refractive index of the object.

There is further provided in accordance with a preferred embodiment of the present invention a method for utilizing differential interference contrast images to provide three-dimensional refractive index information including performing line integration on differential interference contrast images displaying a directional derivative of refractive index of an object to invert the directional derivative thereof, thereby providing a plurality of two-dimensional representations of the refractive index of the object. Alternatively the three-dimensional refractive index map can be obtained from phase microscopy, or from fluorescence where the staining is proportional to the refractive index increment.

Additionally in accordance with a preferred embodiment of the present invention there is provided a method for utilizing differential interference contrast images to provide three-dimensional refractive index information and also including performing deconvolution of the plurality of two-dimensional representations of the refractive index of the object, thereby reducing out-of-focus contributions to the two-dimensional representations of the refractive index of the object. Again, the three-dimensional refractive index map can be obtained from phase microscopy, or from fluorescence where the staining is proportional to the refractive index increment.

Further in accordance with a preferred embodiment of the present invention there is provided apparatus for ray tracing through a medium having multiple variations in refractive index including:

a computer employing an analytically determined path of a ray through the multiplicity of locations in the medium, for a plurality of rays impinging thereon in different directions, by utilizing known local variation of the refractive index at a multiplicity of locations in the medium.

There is additionally provided in accordance with a preferred embodiment of the present invention a method of ray tracing through a medium having multiple variations in refractive index including:

determining local variation of the refractive index at a multiplicity of locations in the medium;

analytically determining the path of a ray through the multiplicity of locations in the medium, for a plurality of rays impinging thereon in different directions. The ray tracing may also include the computation of absorptions, reflections and scattering of rays and their contributions to the imaging process.

Still further in accordance with a preferred embodiment of the present invention there is provided apparatus for confocal microscopy including:

a ray tracer, employing known variations of the refractive index in a three-dimensional sample for determining the paths of a multiplicity of rays emerging from at least one point in the sample and passing through the sample, thereby determining an aberrated wavefront for each the point; and

an adaptive optics controller utilizing the aberrated wavefront to control an adaptive optical element in a confocal microscope, thereby to correct aberrations resulting from the variations in the refractive index.

There is additionally provided in accordance with a preferred embodiment of the present invention a method for confocal microscopy including:

determining variations of the refractive index in a three-dimensional sample;

determining the paths of a multiplicity of rays emerging from at least one point in the sample and passing through the sample, thereby determining an aberrated wavefront for each the point; and

utilizing the aberrated wavefront to control an adaptive optical element in a confocal microscope, thereby to correct aberration resulting from the variations in the refractive index.

There is additionally provided in accordance with a preferred embodiment of the present invention a method for adding (computationally or physically) in the imaging path a three-dimensional medium (anti-sample) with refractive properties that correct for the distortions of the three-dimensional sample.

BRIEF DESCRIPTION OF THE DRAWINGS

The present invention will be understood and appreciated more fully from the following detailed description, taken in conjunction with the drawings in which:

Figs. 1A and 1B are respectively representations of three dimensional microscopic images of an object according to the prior art and in accordance with the present invention;

Fig. 2 is a simplified partially pictorial, partially block diagram illustration of apparatus for computational adaptive imaging constructed and operative in accordance with a preferred embodiment of the present invention;

Fig. 3 is a simplified flow chart of the operation of the apparatus for computational adaptive imaging of Fig. 2;

Fig. 4 is a simplified diagram of line integration functionality which is carried out by the apparatus of Fig. 2;

Fig. 5 is a simplified diagram of ray tracing functionality which is carried out by the apparatus of Fig. 2;

Fig. 6 is a simplified diagram of wavefront integration functionality which is carried out by the apparatus of Fig. 2; and

Fig. 7 is a simplified flow chart illustrating deconvolution functionality which is carried out by the apparatus of Fig. 2.

DETAILED DESCRIPTION OF THE INVENTION

Reference is now made to Figs. 1A and 1B, which are respectively representations of three dimensional microscopic images of an object according to the prior art and in accordance with the present invention.

It is known in the prior art to image a point source or a collection of point sources in an ideal sample displaying no substantial variation in refractive index. When an ideal optical system is focussed at slightly different depths in the sample, a three dimensional image appears, including a plurality of two-dimensional diffraction limited images designated by Roman numerals I, II, III, IV and V in Fig. 1A. The prior art, described, inter alia in the aforesaid Agard et al 1989 reference is capable of

deconvoluting the plurality of two-dimensional images I - V to a deconvoluted three dimensional image, including a single in focus two-dimensional image VI, which contains substantially all of the image intensity from images I - V and a plurality of out of focus two-dimensional images which substantially contain no image intensity.

The prior art, however, does not know how to deal adequately with samples which display substantial variation in refractive index.

The present invention provides a solution to this problem, as illustrated in Fig. 1B which shows images of a non-ideal sample, such as a biological sample, displaying substantial variation in refractive index. When an ideal optical system is focussed at slightly different depths in the non-ideal sample, a three-dimensional image appears, including a plurality of two-dimensional diffraction limited images designated by Roman numerals I, II, III, IV and V in Fig. 1B. In contrast to the images appearing in Fig. 1A, it is seen that these images are extremely non-uniformly distorted due to variations in the refractive index at various locations in the sample.

The present invention, as will be described hereinbelow, is capable of deconvoluting the plurality of two-dimensional images I - V in Fig. 1B, notwithstanding their great distortions due to variations in the refractive index at various locations in the sample, to a substantially non-distorted, deconvoluted three-dimensional image, including a single in-focus two-dimensional image VI, which contains substantially all of the image intensity from images I - V and a plurality of out-of- focus two-dimensional images which substantially contain no image intensity.

Reference is now made to Fig. 2, which is a simplified partially pictorial, partially block diagram illustration of apparatus for computational adaptive imaging constructed and operative in accordance with a preferred embodiment of the present invention. The apparatus of Fig. 2 typically includes a conventional computer-controlled optical microscope 10, such as a microscope manufactured by Carl Zeiss and sold under the name Axioskop. Associated with microscope 10 there are preferably provided computer controlled filter wheels 12 and 14. Filter wheel 12 is disposed downstream of an excitation light source 16, such as a mercury arc lamp, which provides epi-illumination via a computer-controlled shutter 18 and filter wheel 12 to a dichroic

mirror 20 within the microscope 10.

Trans-illumination is provided to a sample 22, typically mounted between two slides 24 and 26, by means of a halogen light source 28 via a computer-controlled shutter 30. Depending on which of shutters 18 and 30 is open, the sample receives trans-illumination or epi-illumination so as to provide either a DIC image or a fluorescent image respectively. It is noted that DIC images conventionally require additional optical elements in the imaging light path, which are omitted from Fig. 2 for the sake of conciseness and clarity.

In accordance with a preferred embodiment of the present invention, the DIC or fluorescent image is received via computer-controlled filter wheel 14 by a digital CCD sensor 32, such as a Photometrics PXL. Preferably a polarizer is included in one of the windows of filter wheel 14 and is employed for DIC imaging.

In accordance with a preferred embodiment of the present invention, the output of the digital CCD sensor 32 is supplied to a computer 34, such as a Silicon Graphics 02 workstation which performs the following functionality:

ray tracing, utilizing information relating to the refractive characteristics in the sample, a multiplicity of rays from a multiplicity of locations in the sample through the sample, thereby providing a location dependent point spread function; and

deconvoluting, utilizing the location dependent point spread function, thereby providing an output image corrected for distortions due to variations in the refractive characteristics in the three-dimensional imaged volume.

Preferably wavefront integration is performed following the ray tracing and prior to the deconvoluting.

In accordance with a preferred embodiment of the present invention, the information relating to the refractive characteristics of the sample is provided by line integration of the DIC image.

Reference is made to Fig. 3, which is a simplified flow chart of the operation of the apparatus for computational adaptive imaging of Fig. 2. As illustrated in Fig. 3, three dimensional images from the microscope 10 and CCD 32, typically include a plurality of observed fluorescent 3D images 40 and a differential interference contrast

(DIC) 3D image 42.

In accordance with a preferred embodiment of the present invention, line integration 44 is performed on the DIC. The line integration preferably provides a 3D refractive index map 46.

In accordance with a preferred embodiment of the present invention, ray tracing 48 is performed on the 3D refractive index map 46 and the resulting wavefront is subject to wavefront integration 50, thus providing a location dependent point spread function (PSF) 52.

In accordance with a preferred embodiment of the present invention, the location dependent PSF is utilized in a deconvolution step 54 which is applied to the observed fluorescent 3D image 40.

In accordance a preferred embodiment of the invention, the deconvolution produces a corrected image, such as the image illustrated at reference VI in Fig. 1B.

Reference is now made to Fig. 4, which is a simplified diagram of line integration functionality which is carried out by the apparatus of Fig. 2. Fig. 4 illustrates a sample, such as a sphere 60 of uniform index of refraction, which differs from that of surrounding media 62. Sample 60 may be taken to represent a nucleus, while the surrounding media may be taken to represent cytoplasm. A scan line 64 illustrates the index of refraction as a function of location along line 65. The characteristic PSF of the microscope 10 operating in the DIC imaging mode is illustrated at reference numeral 66. The PSF is also illustrated by trace 68.

The output image of sample 60 of the CCD sensor 32 operating in a DIC mode is illustrated at reference numeral 70 and also by trace 72. Line integration of the output image produces an image 74 which accurately represents the original sample, seen at reference numerals 60 and 62.

It is appreciated that line integration of DIC images has two complex contributions in reality. One is the accumulation of noise in the integration and the second is the slow contribution of low-intensity out-of-focus contributions. The problem of noise is preferably alleviated by introducing a decay function in the line integration. The out-of-focus contribution can be reduced significantly by deconvoluting the

integrated DIC images.

Reference is now made to Fig. 5, which is a simplified diagram of ray tracing functionality which is carried out by the apparatus of Fig. 2. As seen in Fig. 5, it is seen that an isotropic fan of rays is drawn from every point in an imaged volume, e.g. the sample. These rays are ray traced such that their paths and phases are modified in accordance with variations in the refractive index of the sample. The result of the ray tracing is an aberrated wavefront for every point in the imaged volume.

Reference is now made to Fig. 6, which is a simplified diagram of prior art wavefront integration functionality which is carried out by the apparatus of Fig. 2. As seen in Fig. 6, for every point in the vicinity of a focus R0, an interference integral is taken over the wavefront. The integrations for all of the points in the vicinity of the focus R0 define the three-dimensional point spread function, as described inter alia in the aforesaid prior art reference to Goodman.

Reference is now made to Fig. 7, which is a simplified flow chart illustrating deconvolution functionality which is carried out by the apparatus of Fig. 2. As seen in Fig. 7, the observed image 80, such as the observed fluorescent 3D image 40 (Fig. 3) is deconvoluted using the point spread function (PSF) calculated as described hereinabove with reference to Figs. 5 and 6. It is appreciated that the location dependent PSF is preferably a multi-resolution PSF. This calculation is preferably performed in an iterative process which endeavors to provide progressively better approximations of the imaged sample.

This iterative process typically proceeds by initially defining a guessed object 82, which typically is identical to the observed image. The guessed object is convoluted with a location dependent point spread function 84, such as that derived by ray tracing and wavefront integration (Fig. 3) to produce a blurred image 86. This blurred image is compared with the observed image and a correction based on the comparison is iteratively applied to the guessed object. Following multiple iterations, the guessed object constitutes the corrected 3D image of the sample in accordance with a preferred embodiment of the present invention.

Additional technical descriptions of a preferred embodiment of the

invention appear in the following article by the inventor Z. Kam: "Microscopic Differential Interference Contrast Image Processing by Line Integration (LID) and Deconvolution". Bioimaging 6 (4): 166-176 (1998).

It will be appreciated by persons skilled in the art that the present invention is not limited to what has been particularly shown and described hereinabove. Rather the scope of the present invention includes both combinations and subcombinations of the various features described hereinabove as well as modifications and additions thereto which would occur to a person of skill in the art upon reading the foregoing description and which are not in the prior art.

CLAIMS

We claim:

1. Apparatus for computational adaptive imaging including:

an image information acquirer providing information relating to the refractive characteristics in a three-dimensional imaged volume;

a ray tracer, utilizing the information relating to the refractive characteristics to trace a multiplicity of rays from a multiplicity of locations in the three-dimensional imaged volume through the three-dimensional imaged volume, thereby providing a location dependent point spread function; and

a deconvolver, utilizing the location dependent point spread function, to provide an output image corrected for distortions due to variations in the refractive characteristics in the three-dimensional imaged volume.

2. Apparatus according to claim 1 wherein the acquirer is adapted to obtain refractive index information from DIC, for example from phase microscopy or from fluorescence.

3. Apparatus according to claim 1 wherein the acquirer is adapted to utilize previously determined refractive characteristics.

4. Apparatus for computational adaptive imaging according to claim 1 and wherein the image information acquirer acquires at least two three-dimensional images of a three-dimensional imaged volume, at least one of the two three-dimensional images containing the information relating to the refractive characteristics in a three-dimensional imaged volume.

5. Apparatus according to claim 4 and wherein the image acquirer acquires at least three three-dimensional images of the three-dimensional imaged volume.

6. Apparatus according to claim 4 and wherein the image acquirer acquires a

plurality of three-dimensional images of the three-dimensional imaged volume, each the image having a discrete wavelength band.

7. Apparatus according to claim 4 and wherein the image acquirer acquires a multiplicity of three-dimensional images of the three-dimensional imaged volume, each the image having a wavelength band which is part of a continuum represented by the wavelength bands of the multiplicity of three-dimensional images.

8. Apparatus according to claim 4 wherein the image acquirer acquires a single three-dimensional image of the three-dimensional image volume.

9. Apparatus according to claim 4 and wherein the ray tracer and the deconvolver utilize the information relating to the refractive characteristics in a three-dimensional imaged volume obtained from one of the three-dimensional images to correct at least another one of the three-dimensional images.

10. Apparatus according to claim 9 wherein the ray tracer includes effects on the image of absorptions, reflections and scattering in the sample.

11. Apparatus according to claim 1, and wherein the three-dimensional images are electromagnetic energy images.

12. Apparatus according to claim 11 and wherein the three-dimensional images are infrared images.

13. Apparatus according to claim 1, and wherein the three-dimensional images are non-electromagnetic images.

14. Apparatus according to claim 1, and wherein the image acquirer receives digital image data from a digital image source and derives therefrom the information

relating to the refractive characteristics in a three-dimensional imaged volume.

15. Apparatus according to claim 1, and wherein the image acquirer, the ray tracer and the deconvolver operate repeatedly over time to provide a multiplicity of output images, each corrected for distortions due to variations in the refractive characteristics in the three-dimensional imaged volume.

16. Apparatus according to claim 1, and wherein the output image is an acoustic image and the refractive characteristics are characteristics of a material which the passage of acoustic energy therethrough.

17. Apparatus according to claim 1, and wherein the output image is an electromagnetic image and the refractive characteristics are characteristics of a material which the passage of electromagnetic energy therethrough.

18. A method for computational adaptive imaging including the steps of:

providing information relating to the refractive characteristics in a three-dimensional imaged volume;

ray tracing, utilizing the information relating to the refractive characteristics, a multiplicity of rays from a multiplicity of locations in the three-dimensional imaged volume through the three-dimensional imaged volume, thereby providing a location dependent point spread function; and

deconvoluting, utilizing the location dependent point spread function, thereby providing an output image corrected for distortions due to variations in the refractive characteristics in the three-dimensional imaged volume.

19. A method according to claim 18, for adding in the imaging path a three-dimensional medium (anti-sample) with refractive properties that correct for the distortions of the three-dimensional sample.

20. A method for computational adaptive imaging according to claim 18 and wherein the step of providing information includes acquiring at least two three-dimensional images of a three-dimensional imaged volume, at least one of the two three-dimensional images containing the information relating to the refractive characteristics in a three-dimensional imaged volume.

21. A method according to claim 20 and wherein the step of providing information includes acquiring at least three three-dimensional images of a three-dimensional imaged volume.

22. A method according to claim 20 and wherein the step of providing information includes acquiring a plurality of three-dimensional images of the three-dimensional imaged volume, each the image having a discrete wavelength band.

23. A method according to claim 20 and wherein the step of providing information includes acquiring a multiplicity of three-dimensional images of the three-dimensional imaged volume, each the image having a wavelength band which is part of a continuum represented by the wavelength bands of the multiplicity of three-dimensional images.

24. A method according to claim 18, and wherein the three-dimensional images are electromagnetic energy images.

25. A method according to claim 24 and wherein the three-dimensional images are infrared images.

26. A method according to claim 18, and wherein the three-dimensional images are non-electromagnetic images.

27. A method according to claim 18, and wherein the step of providing

includes receiving digital image data from a digital image source and deriving therefrom the information relating to the refractive characteristics along a multiplicity of light paths in a three-dimensional imaged volume.

28. A method according to claim 18, and wherein the steps of providing information, ray tracing and deconvoluting operate repeatedly over time to provide a multiplicity of output images, each corrected for distortions due to variations in the refractive characteristics in the three-dimensional imaged volume.

29. A method according to claim 28 wherein the refractive characteristics are estimated.

30. Apparatus for utilizing differential interference contrast images to provide three-dimensional refractive index information including a line integrator operating on differential interference contrast images displaying a directional derivative of refractive index of an object to invert the directional derivative thereof, thereby providing a plurality of two-dimensional representations of the refractive index of the object.

31. Apparatus for utilizing differential interference contrast images to provide three-dimensional refractive index information according to claim 30 and also including a deconvolver performing deconvolution of the plurality of two-dimensional representations of the refractive index of the object, thereby reducing out-of-focus contributions to the two-dimensional representations of the refractive index of the object.

32. A method for utilizing differential interference contrast images to provide three-dimensional refractive index information including performing line integration on differential interference contrast images displaying a directional derivative of refractive index of an object to invert the directional derivative thereof, thereby providing a plurality of two-dimensional representations of the refractive index of the object.

33. A method for utilizing differential interference contrast images to provide three-dimensional refractive index information according to claim 32 and also including performing deconvolution of the plurality of two-dimensional representations of the refractive index of the object, thereby reducing out-of-focus contributions to the two-dimensional representations of the refractive index of the object.

34. Apparatus for ray tracing through a medium having multiple variations in refractive index including:

a computer employing an analytically determined path of a ray through the multiplicity of locations in the medium, for a plurality of rays impinging thereon in different directions, by utilizing known local variation of the refractive index at a multiplicity of locations in the medium.

35. A method of ray tracing through a medium having multiple variations in refractive index including:

determining local variation of the refractive index at a multiplicity of locations in the medium;

analytically determining the path of a ray through the multiplicity of locations in the medium, for a plurality of rays impinging thereon in different directions.

36. Apparatus for confocal microscopy including:

a ray tracer, employing known variations of the refractive index in a three-dimensional sample for determining the paths of a multiplicity of rays emerging from at least one point in the sample and passing through the sample, thereby determining an aberrated wavefront for each the point; and

an adaptive optics controller utilizing the aberrated wavefront to control an adaptive optical element in a confocal microscope, thereby to correct aberrations resulting from the variations in the refractive index.

37. A method for confocal microscopy including:

determining variations of the refractive index in a three-dimensional sample;

determining the paths of a multiplicity of rays emerging from at least one point in the sample and passing through the sample, thereby determining an aberrated wavefront for each the point; and

utilizing the aberrated wavefront to control an adaptive optical element in a confocal microscope, thereby to correct aberrations resulting from the variations in the refractive index.

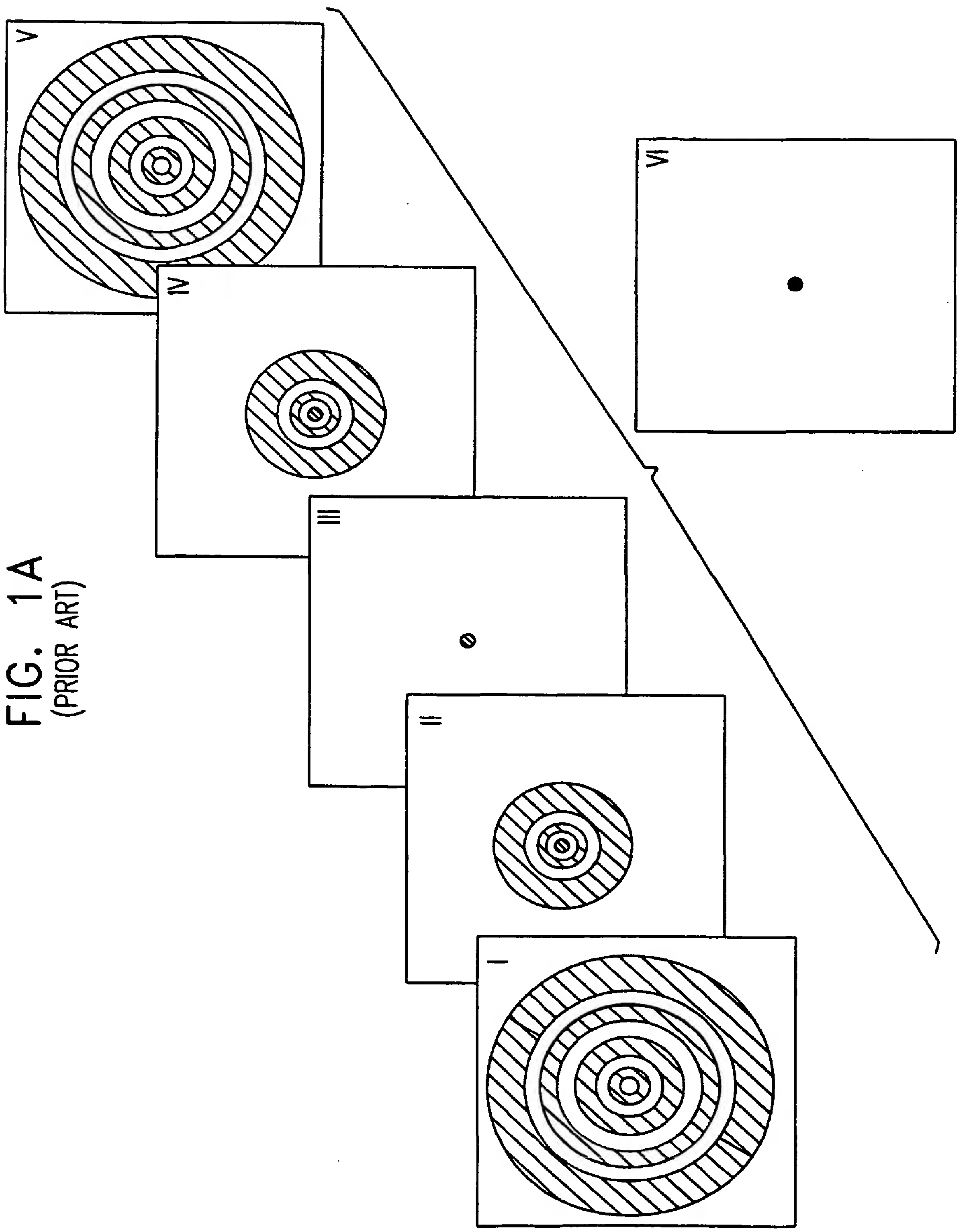


FIG. 1A
(PRIOR ART)

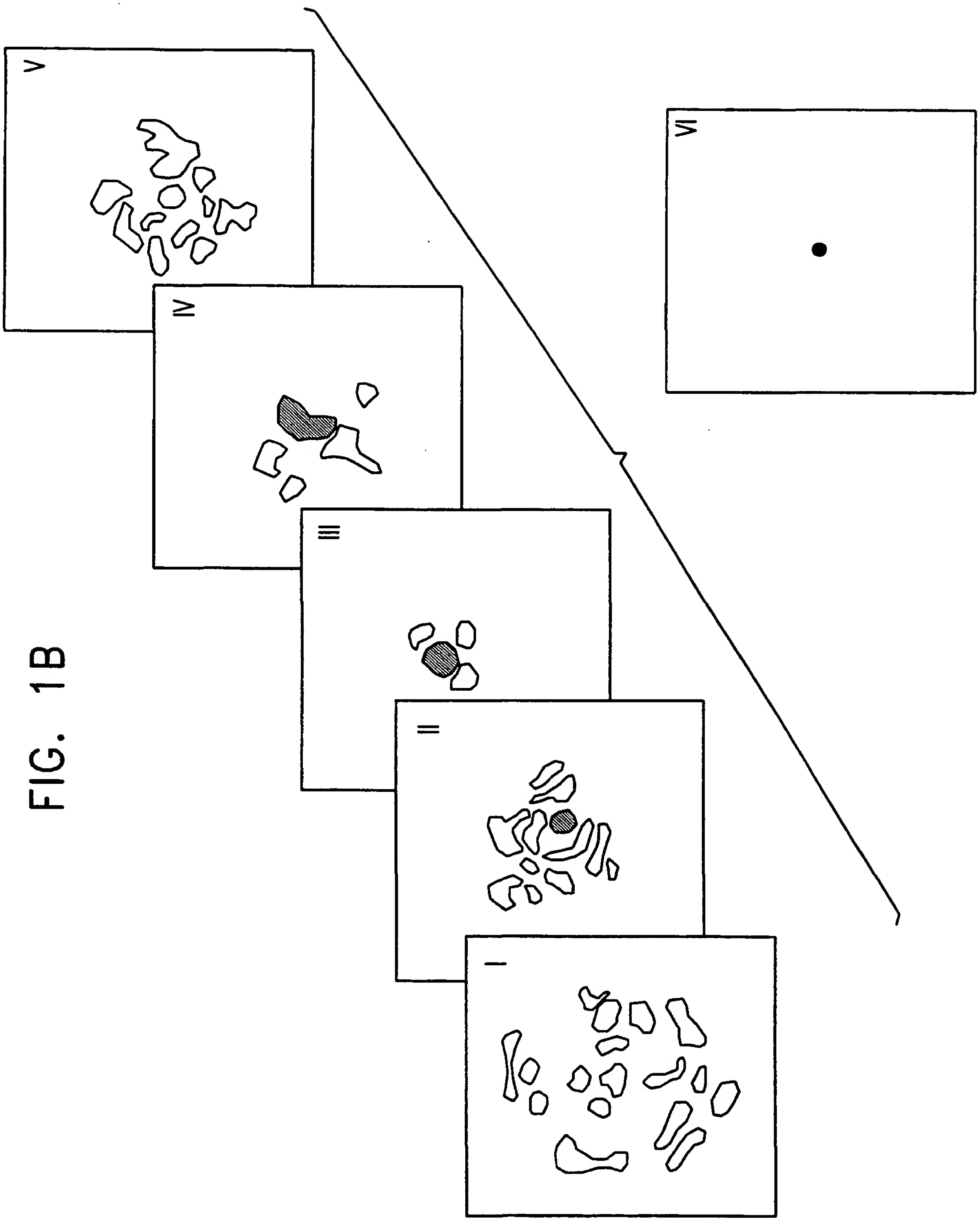
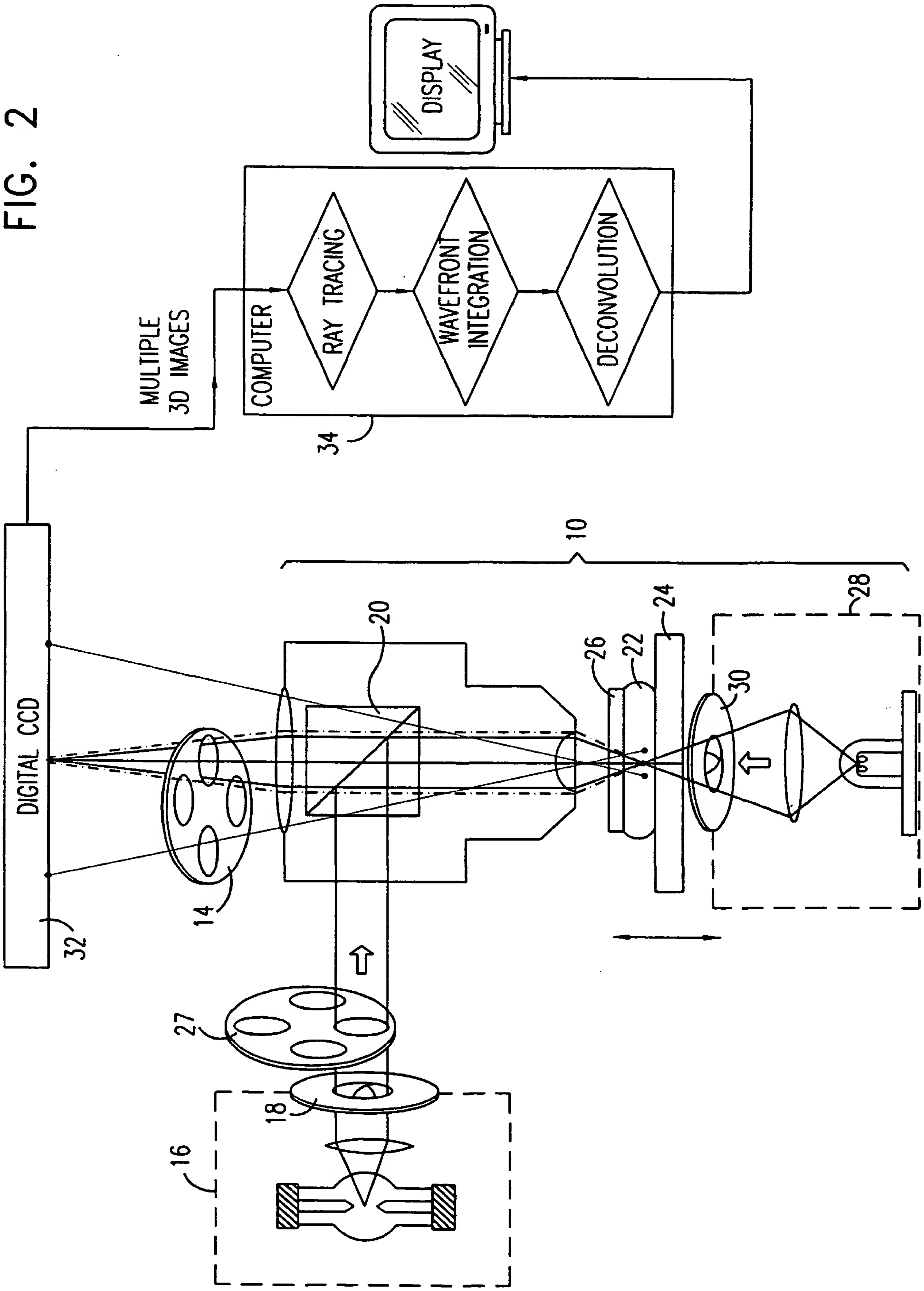


FIG. 1B

FIG. 2


DISPLAY
COMPUTER
RAY TRACING
WAVEFRONT INTEGRATION
DECONVOLUTION
34
MULTIPLE 3D IMAGES
DIGITAL CCD
32
14
20
10
24
22
26
28
30
27
18
16

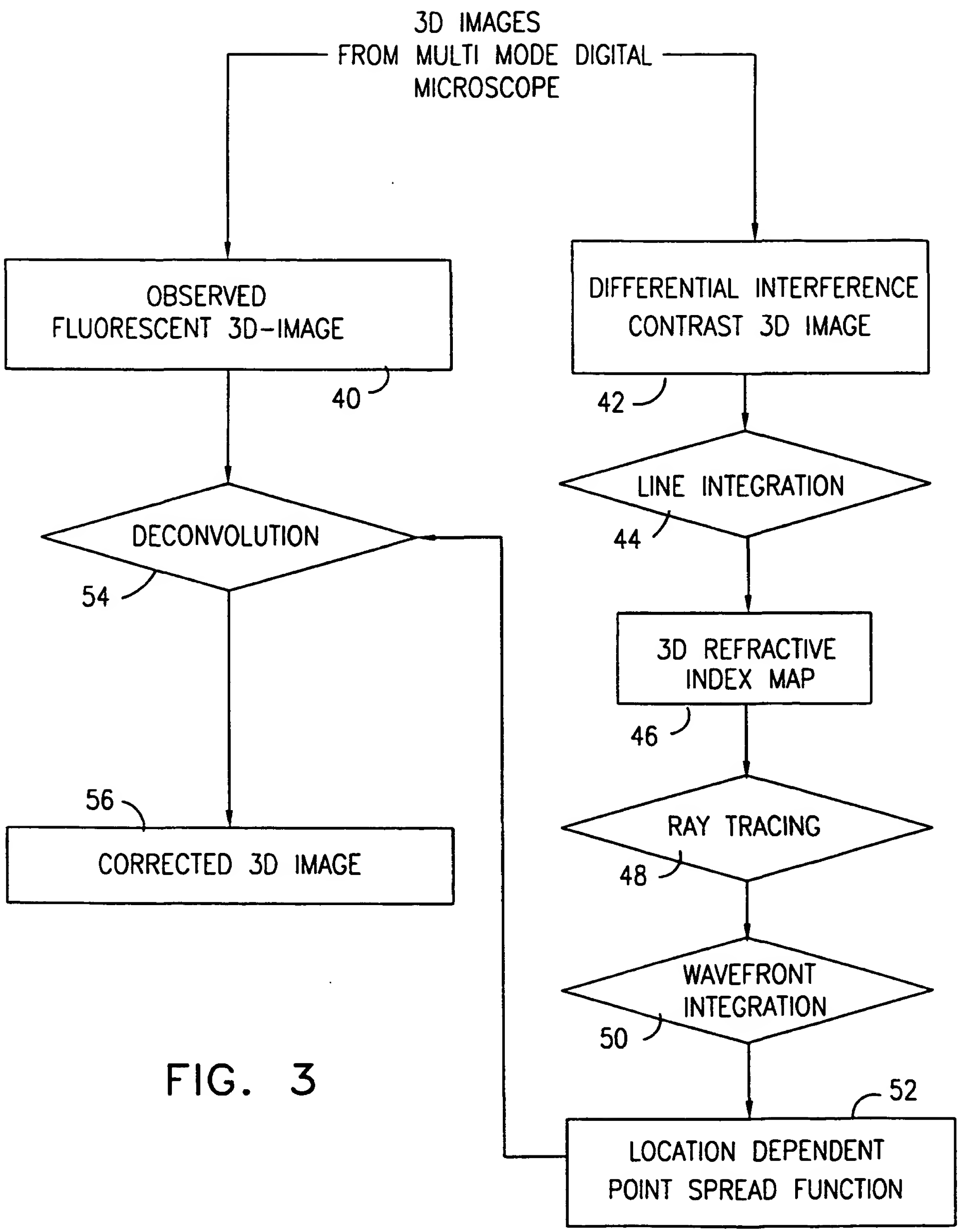

3D IMAGES
FROM MULTI MODE DIGITAL
MICROSCOPE
OBSERVED
FLUORESCENT 3D-IMAGE
40
DIFFERENTIAL INTERFERENCE
CONTRAST 3D IMAGE
42
LINE INTEGRATION
44
DECONVOLUTION
54
3D REFRACTIVE
INDEX MAP
46
RAY TRACING
48
56
CORRECTED 3D IMAGE
WAVEFRONT
INTEGRATION
50
52
LOCATION DEPENDENT
POINT SPREAD FUNCTION

FIG. 3

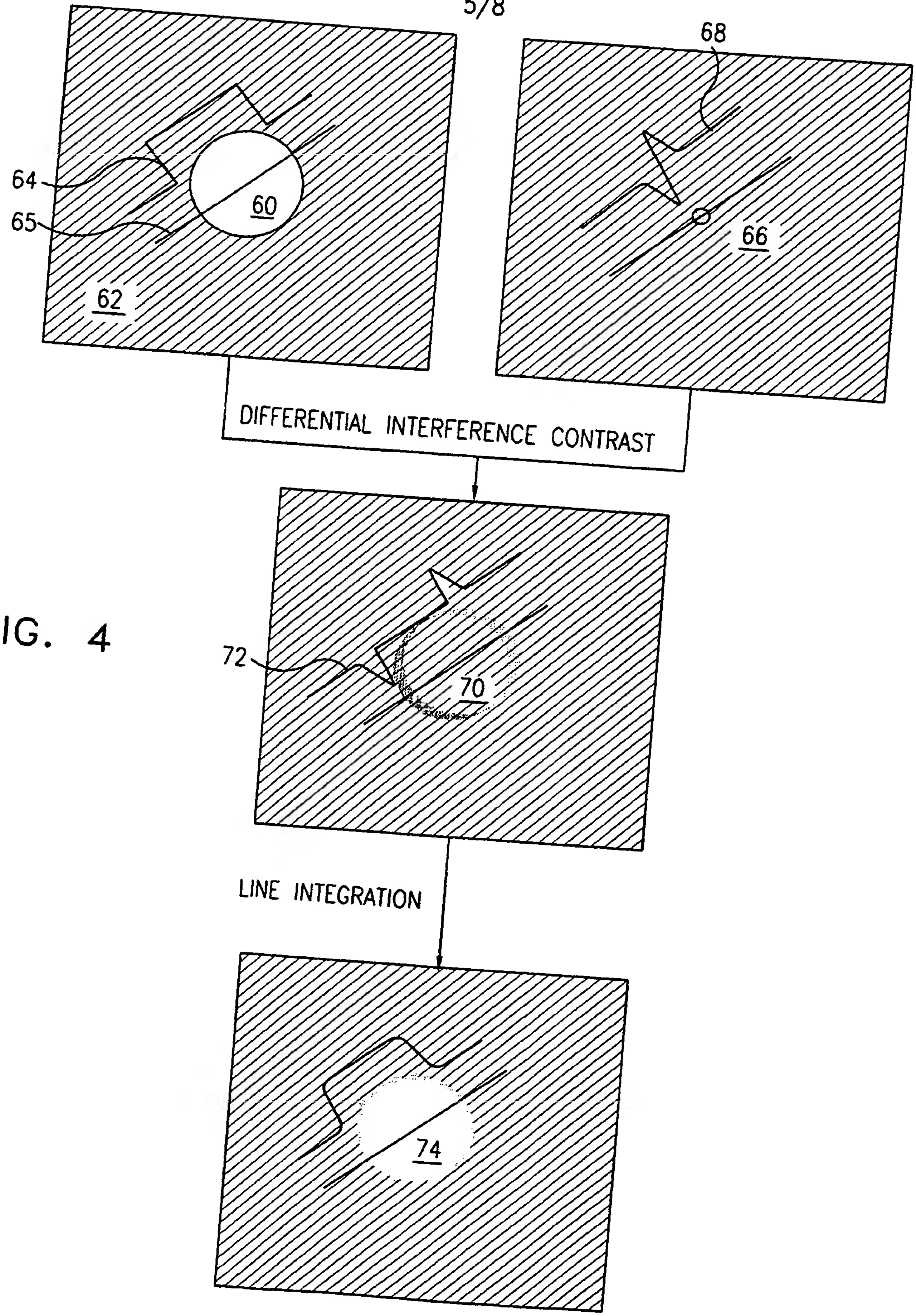

64
65
60
62
68
66
DIFFERENTIAL INTERFERENCE CONTRAST
72
70
LINE INTEGRATION
74

FIG. 4

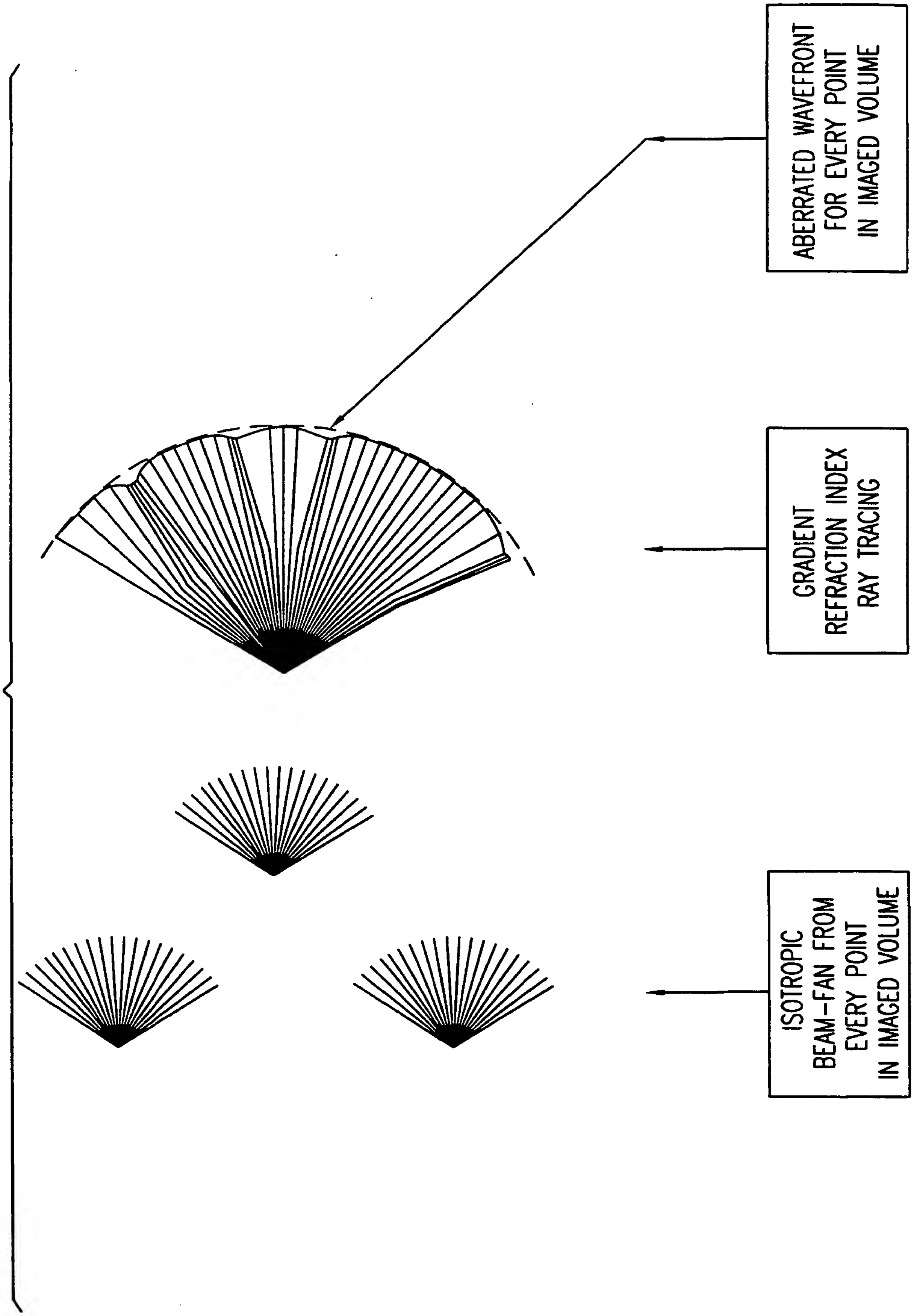

ABERRATED WAVEFRONT FOR EVERY POINT IN IMAGED VOLUME
GRADIENT REFRACTION INDEX RAY TRACING
ISOTROPIC BEAM-FAN FROM EVERY POINT IN IMAGED VOLUME

FIG. 5

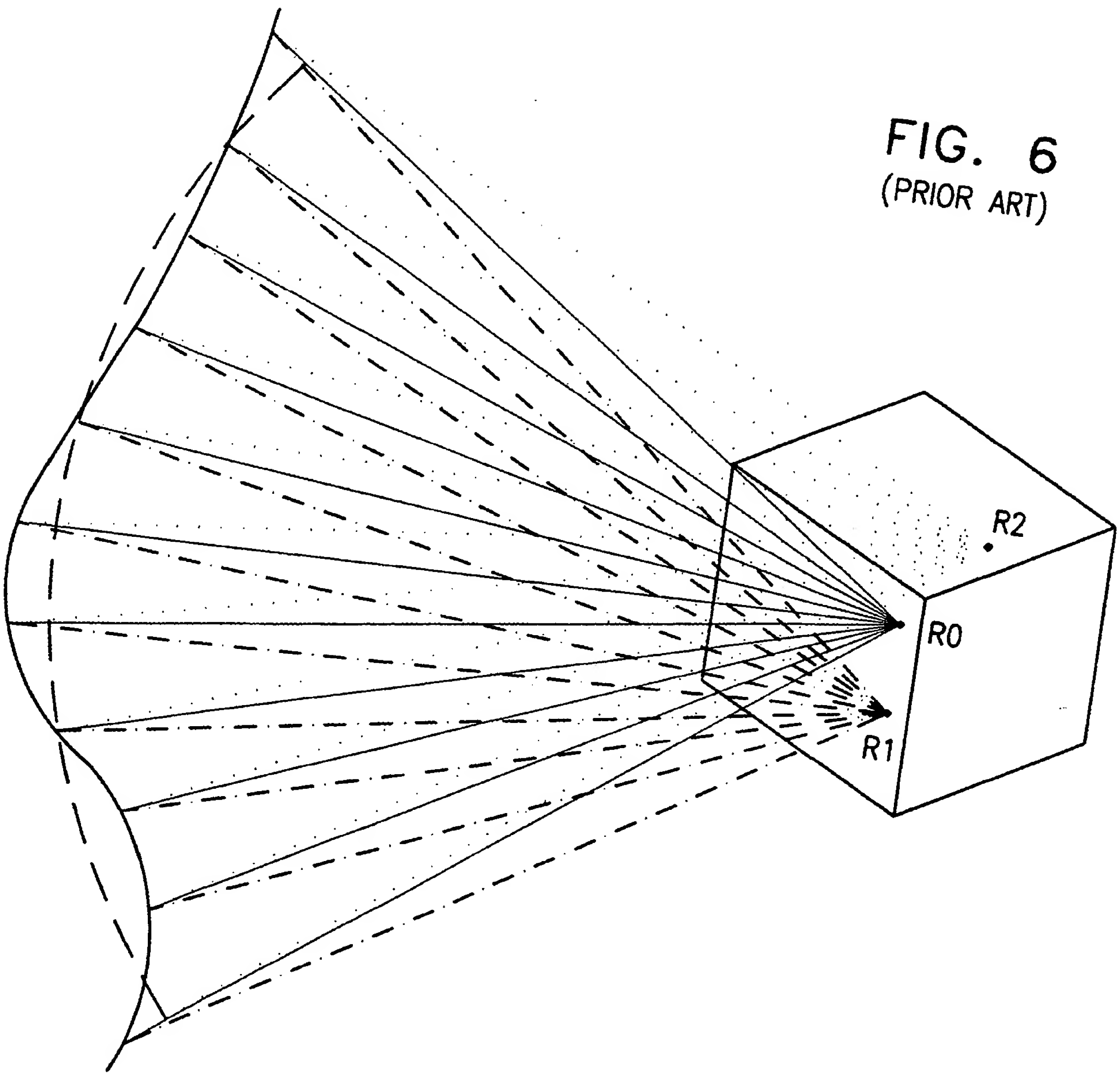
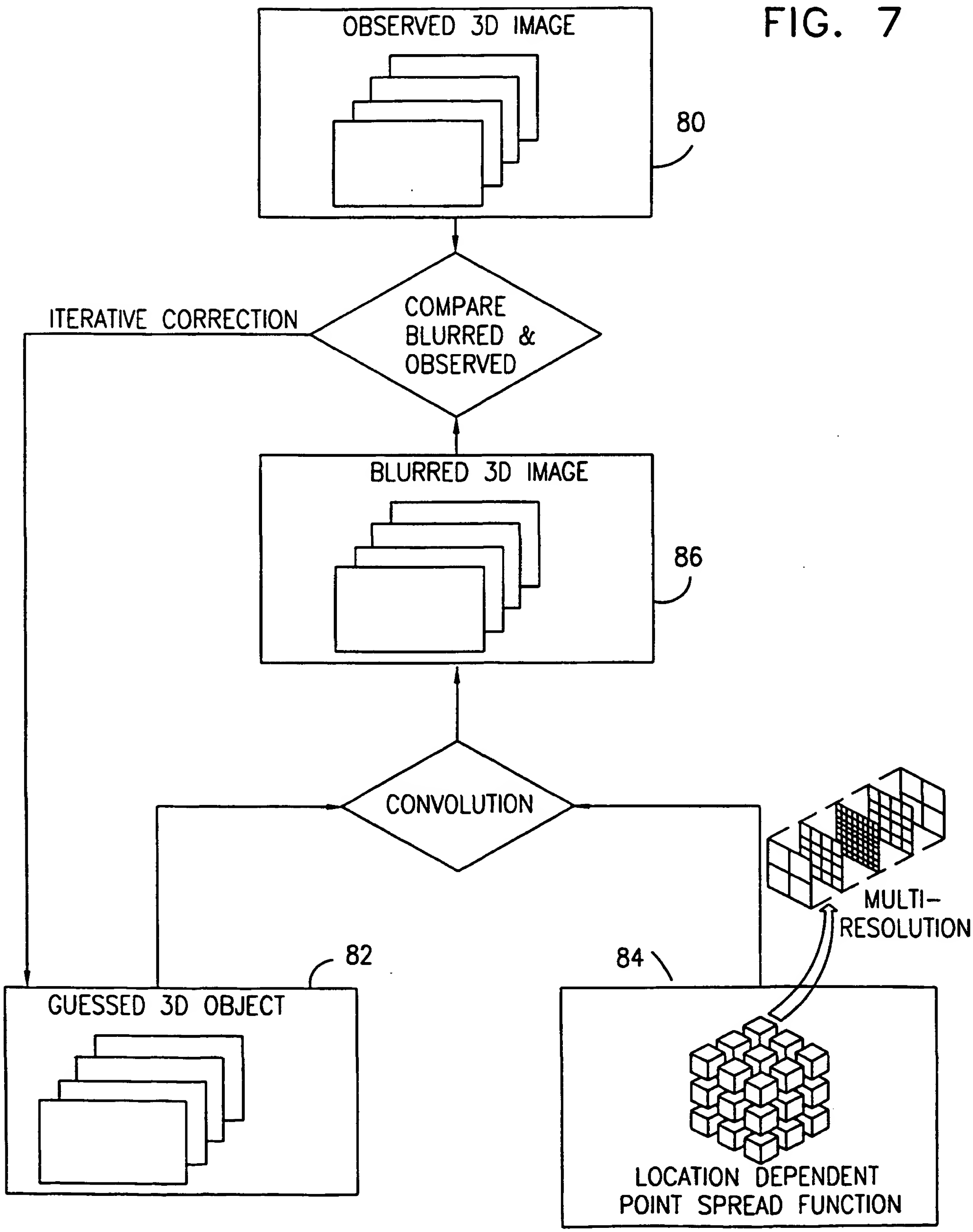


FIG. 6
(PRIOR ART)

FIG. 7


OBSERVED 3D IMAGE
80
COMPARE BLURRED & OBSERVED
ITERATIVE CORRECTION
BLURRED 3D IMAGE
86
CONVOLUTION
MULTI-RESOLUTION
82
GUESSED 3D OBJECT
84
LOCATION DEPENDENT POINT SPREAD FUNCTION

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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09/238,225	27 January 1999 (27.01.99)	US

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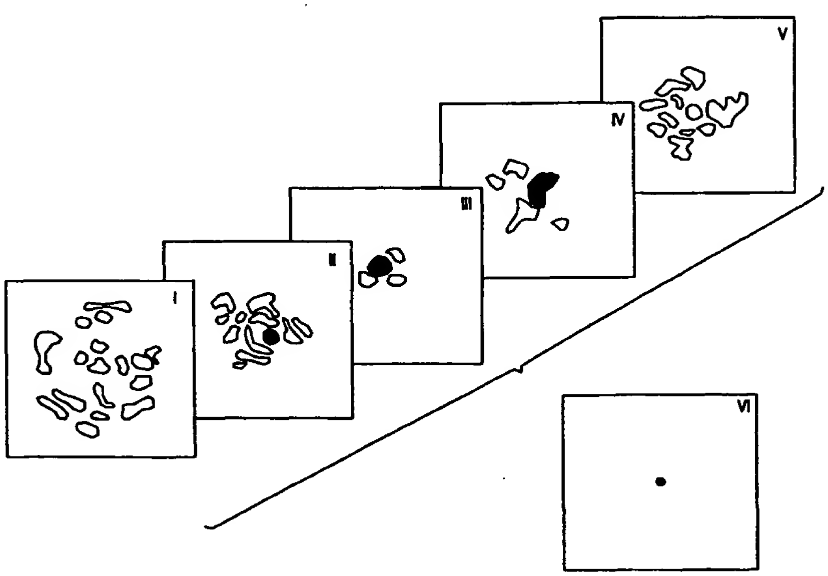
(54) Title: COMPUTERIZED ADAPTIVE IMAGING



(57) Abstract

Apparatus for computational adaptive imaging comprises the following: an image information acquirer, which provides information relating to the refractive characteristics in a three-dimensional imaged volume; a ray tracer, which uses the information relating to the refractive characteristics to trace a multiplicity of rays from a multiplicity of locations in the three-dimensional imaged volume through the three-dimensional imaged volume, thereby providing a location dependent point spread function, and a deconvolver, which uses the location dependent point spread function, to provide an output image corrected for distortions due to variations in the refractive characteristics in the three-dimensional imaged volume.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/IL 99/00645

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G06T1/00 G02B21/14 G02B21/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 G06T G02B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GB 2 321 968 A (INST FRANCAIS DU PETROL) 12 August 1998 (1998-08-12) page 4, line 11 -page 5, line 1 page 9, line 9 -page 18, line 16 ---	1,13,16, 18,26
A	US 5 671 136 A (WILLHOIT JR LOUIS E) 23 September 1997 (1997-09-23) abstract; figures 3,4 column 14, line 66 -column 15, line 7 --- -/--	1,13,16, 18,26

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
16 March 2000	22.06.00

Name and mailing address of the ISA	Authorized officer
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International Application No
PCT L 99/00645

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	B.A. SCALETTAR ET AL: "Dispersion, abberation and deconvolution in multi-wavelength fluorescence images" JOURNAL OF MICROSCOPY, vol. 182, no. 1, April 1996 (1996-04), pages 50-60, XP000879385 cited in the application page 50, left-hand column page 57, left-hand column, last paragraph -page 59	1,2,10, 14, 17-19,24
A	US 5 787 146 A (GIEBELER ROBERT H) 28 July 1998 (1998-07-28) column 10, line 38 -column 12, line 5	1,11,17, 18,24
A	PATENT ABSTRACTS OF JAPAN vol. 1997, no. 08, 29 August 1997 (1997-08-29) & JP 09 105864 A (OLYMPUS OPTICAL CO LTD), 22 April 1997 (1997-04-22) abstract & US 5 969 855 A (ITOH MASAHIDE ET AL.) 19 October 1999 (1999-10-19) column 2, line 65 -column 3, line 3 column 4, line 1 - line 26	1,2,11, 17,18,24
A	AGARD D A ET AL: "Three-dimensional microscopy: image processing for high resolution subcellular imaging" NEW METHODS IN MICROSCOPY AND LOW LIGHT IMAGING, SAN DIEGO, CA, USA, 8-11 AUG. 1989, vol. 1161, pages 24-30, XP000879382 Proceedings of the SPIE - The International Society for Optical Engineering, 1989, USA ISSN: 0277-786X cited in the application page 24 -page 25, paragraph 2 page 27, paragraph 2	1,11,18, 24
P,A	KAM Z: "MICROSCOPIC DIFFERENTAIL INTERFERENCE CONTRAST IMAGE PROCESSING BY LINE INTEGRATION (LID) AND DECONVOLUTION" BIOIMAGING,GB,IOP PUBLISHING, vol. 6, no. 4, December 1998 (1998-12), pages 166-176, XP000879404 ISSN: 0964-1726 cited in the application the whole document	1-37

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL 99/00645

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet(s)

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-29

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/IL 99/00645

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 1-29

   Apparatus for computational adaptive imaging including an image information acquirer, a ray tracer providing a location dependent point spread function and a deconvolver utilizing the location dependent point spread function to provide a corrected output image.

2. Claims: 30-33

   Apparatus and method for utilizing differential interference contrast images to provide three-dimensional refractive index information including a line integrator and a directional derivative

3. Claims: 34-35

   Apparatus and method for ray tracing through a medium having multiple variations in refractive index including the determination of the refractive index at a multiplicity of locations in the medium

4. Claims: 36-37

   Apparatus for confocal microscopy including a ray tracer and adaptive optics

INTERNATIONAL SEARCH REPORT

mation on patent family members

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB 2321968 A	12-08-1998	FR 2759172 A	07-08-1998
		CA 2226389 A	05-08-1998
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		WO 9722077 A	19-06-1997
US 5787146 A	28-07-1998	NONE	
JP 09105864 A	22-04-1997	US 5969855 A	19-10-1999